MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

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SUBJECT: OPDRA Postmarketing Safety Review:
Drugs : Etodolac (Lodine, NDA 18-922, 20-584)
Celecoxib (Celebrex, NDA 20-998)
Rofecoxib (Vioxx, NDA 21-042, 21-052)
Reaction: Renal Failure

EXECUTIVE SUMMARY

This review of U.S. postmarketing reports of renal failure associated with the use of celecoxib and rofecoxib was provided in response to your request and in preparation for the upcoming Advisory Committee meeting in February 2001. In review of GI events for this meeting, we noticed several reports of renal failure prompting this in-depth case review. We also summarized reports of renal failure for an anti-inflammatory drug etodolac for your information.

Renal concerns are addressed in the labeling under the *Clinical Pharmacology, Warnings, Precautions, and Adverse Reactions* sections, with some variation in wording and emphasis for each drug. As stated in the recent labeling, patients at greatest risk of renal toxicity are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. We evaluated a total of 277 U.S. cases of renal failure possibly associated with the 3 drugs, etodolac (13), celecoxib (122) and rofecoxib (142). Generally, the cases occurred in high-risk elderly patients with a mean age of 70-76 and mostly in females (62-77%). Almost all of the cases occurred with recommended doses. The mean time to onset of renal failure was between 27-42 days (median 10-28 days). Of interest, 32

of 100 cases that reported time to onset (32%) of rofecoxib renal failure cases occurred acutely within 3 days of starting therapy. The mean creatinine changes from baseline when reported ranged from 2.7 to 4.0. Over 70% of cases were hospitalized for treatment, including dialysis and death as a result.

Common multiple risk factors in these cases included concurrent/underlying medical diseases such as hypertension, diabetes, congestive heart failure, or pre-existing renal disease, and concomitant use of diuretics or ACE inhibitors.

In conclusion, cases of serious life threatening renal failure have been reported associated with etodolac, celecoxib and rofexocib based on postmarketing data. Renal failure mostly occurred at recommended doses and in some cases shortly after drug treatment in patients with or without risk factors.

DRUG INFORMATION and LABELING

Etodolac (Lodine®), celecoxib (Celebrex®), and rofecoxib (Vioxx®) are nonsteroidal anti-inflammatory drugs (NSAIDs) that were approved by the FDA in January 1991, December 1998, and May 1999, respectively. The mechanism of action of NSAIDs is primarily by interfering with the enzymatic activity of cyclooxygenase (COX), thereby inhibiting the production of prostaglandin from arachidonic acid. Prostaglandin in the kidneys regulates intrarenal blood flow and electrolyte balance.

Two COX isoenzymes have been identified: COX-1 and COX-2. Hypotheses that prostaglandins produced by the COX-2 dependent pathway result in pain, inflammation, and tissue destruction led to the development of agents that selectively inhibit the COX-2 isoform. To date, two agents are commercially available in the U.S. that mainly inhibit the COX-2 but not the COX-1 isoenzyme at recommended doses: celecoxib and rofecoxib. Etodolac is a nonspecific NSAID that inhibits both COX-1 and COX-2.

Lodine is indicated for acute and long-term management of signs and symptoms of rheumatoid and osteoarthritis, as well as for pain management. Celebrex is indicated for the relief of signs and symptoms of osteoarthritis and rheumatoid arthritis in adults. It is also indicated to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis, as an adjunct to standard therapy. Vioxx is indicated for the relief of signs and symptoms of osteoarthritis, management of acute pain in adults, and treatment of primary dysmenorrhea.

Labeling for **Vioxx** is shown below and is similar for all 3 products with regard to renal concerns. The information is found under the Clinical Pharmacology, Warnings, Precautions, and Adverse Reactions sections of the current label.

Clinical Pharmacology, *Renal Insufficiency*
In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While

renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX in these patients.

Warnings, *Advanced Renal Disease*
No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable.

Precautions, *Renal Effects*
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range.

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease.

Adverse Reactions
Urogenital System: acute renal failure, breast malignant neoplasm, *interstitial nephritis*, prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure.*

The Vioxx advises the patient to inform the physician of kidney disease and mentions the following in the section titled, *What are the possible side effects of VIOXX*: serious kidney problems occur rarely, including acute kidney failure and worsening of chronic kidney failure. Information for Patient of Vioxx does not mention similar warning. There is no Celebrex Information for Patients section in the labeling.

The labeling for celecoxib is similar to rofecoxib as stated above. However, *worsening chronic renal failure* is not included in the Adverse Reactions section.

We note that the labeling for etodolac differs between Lodine tablets and capsules and Lodine XL Extended Release Tablets. The labeling for Lodine XL Extended Release Tablets regarding renal concerns is similar to celecoxib. Like celecoxib, the labeling for Lodine XL Extended Release Tablets does not mention worsening chronic renal failure in the *Adverse Reactions* section. Unlike Lodine XL Extended Release Tablets, the labeling for Lodine tablets and capsules does not contain a cautionary

statement in the *Clinical Pharmacology* section about use of Lodine in patients with renal impairment. Unlike Lodine XL Extended Release Tablets, the *Warnings* section for Lodine tablets and capsules does not advise against use of Lodine in patients with advanced renal disease. Unlike Lodine XL Extended Release Tablets, the *Precautions* section for Lodine tablets and capsules presents information regarding renal injury in rats, not humans.

Literature

At least one article has appeared in the medical literature describing reversible renal failure in association with celecoxib.[1] The authors hypothesize that, in patients with prostaglandin-dependent disease states such as volume depletion, cirrhosis, CHF, nephrosis, and CRF, the COX-2 enzyme may have an important role in prostaglandin production. Thus, in selected individuals, inhibition of COX-2 could lead to deterioration of renal function through elimination of COX-2-dependent prostaglandins.

DRUG USE

Total prescriptions for the first three years of marketing, as well as information on patient gender, race and dosing strengths administered will be presented for Lodine, Celebrex and Vioxx.

RENAL FAILURE CASE DEFINITION

Renal failure is defined in this review as:

- A rise in serum creatinine of ≥ 0.5 mg/dl, if the baseline serum creatinine is ≤ 3.0 mg/dl or
- A rise in serum creatinine of ≥ 1.0 mg/dl, if the baseline serum creatinine is ≥ 3.0 mg/dl or
- A ≥ 20% decline in recovery serum creatinine from peak serum creatinine or
- A peak serum creatinine of ≥ 2 mg/dl and one or more events from the symptom list is mentioned (see below for symptom list) or
- A rise in BUN (> 25 mg/dl) and one or more events from the symptom list is mentioned (see below for symptom list) or
- Any case requiring phosphate binders (ie. calcium, aluminum) or potassium-binding resins (ie. Kayexalate) or sodium bicarbonate (to correct acidosis) or
- Any case requiring dialysis or kidney transplant or
- Any case with reported diagnosis of renal failure or acute renal failure

"Symptom" List

↓ UOP (urinary output), ↑ blood pressure, ↑ potassium (serum K^+ > 5.1 mmol/L), ↓ sodium (serum Na^+ < 135 mmol/L), hyperphosphatemia, metabolic acidosis (serum HCO_3^- < 20 mmol/L), anemia (Hct < 30%), azotemia, uremia, edema, symptoms of CHF

METHOD OF SELECTION OF AERS CASES

To capture all possible cases of renal failure, acute renal failure, renal insufficiency, renal vascular related renal disorder, renal tubular disorder and hypersensitivity related nephropathies we searched in AERS under the following MedDRA midlevel terms-

- Renal failure and impairment (High Level Term)
- Renal vascular and ischaemic conditions (High Level Term)
- Nephropathies (High Level Group Term)

We reviewed a total of 695 reports from the searches to eliminate duplicates and reports that were miscoded or did not have the events of interest. Most of the cases were renal failure-related events with small numbers of nephritis and renal necrosis. Due to their small numbers, we did not review further cases of nephritis and renal necrosis but focused on cases of renal failure only. Renal failure cases include reports of renal failure, acute renal failure, or any renal insufficiency with adequate data consistent with the case definition. To review the renal failure cases further (based on available information in the reports), we used the general criteria as in Appendix 1 to exclude cases that were not associated with the drug. The remaining cases can be classified either probably or possibly associated with drug by the general criteria as in Appendix 2. For the purpose of this review, all probable and possible cases were grouped together for analysis.

RESULT OF SELECTION OF CASE SERIES

Etodolac

A search of the AERS database on October 26, 2000 for renal cases based on the search strategy (see Method of Selection of Cases) captured a total of 65 cases for etodolac. A hands-on review of the cases resulted in the exclusion of 35 cases primarily due to duplication, erroneous drug, renal failure exacerbated by concomitant acute disease states (for example, GI bleed, sepsis), or nonspecific renal disorder. Of the remaining 30 cases, 13 matched our case definition for renal failure and are included in the case series for further analysis.

Celecoxib

A search in AERS through October 26, 2000 identified 256 reports of renal events associated with celecoxib based on our search strategy. A hands-on review of these reports identified 122 unduplicated reports of renal failure which met our case definition. Reports of abnormal kidney function, fluid retention, oliguria, renal insufficiency not meeting case definition with adequate lab data available, and renal failure precipitated by concomitant rhabdomyolysis or GI bleed or hepatorenal syndrome were excluded.

Rofecoxib

A search of the AERS database on October 26, 2000 for renal cases based on the aforementioned AERS search strategy (see Method of Selection of Cases) captured a total of 374 cases for Vioxx. A hands-on review of the cases resulted in the exclusion of 168 cases primarily due to duplication, erroneous drug, renal failure exacerbated by concomitant acute disease states (ie. GI bleed, rhabdomyolysis, sepsis), nonspecific renal disorder, or isolated oliguria or fluid retention with no indication of renal failure. Of the remaining 206 cases, 142 matched our case definition for renal failure and are included in the case series for further analysis.

We noted that the original searches for renal events revealed 92 reports of fluid retention in which several reported concurrently with renal failure. Most cases were associated with weight gain, edema, dyspnea, or congestive heart failure.

The final counts of U.S. cases of renal failure by drug we analyzed further are the following:

Etodolac	13
Celecoxib	122
Rofecoxib	142

SUMMARY OF CASES

Summary of cases for each drug case series follows:

Etodolac (13)

Descriptive statistics for the renal failure case series are provided in the attached Table 1. Additional demographics:

Daily dose (based on 8 cases): Range 400-900 mg, median 600 mg, mean-611 mg

Indication:	Osteoarthritis-6, rheumatoid arthritis-1, unspecified arthritis-3, lumbosacral sprain-1, unknown-3
Dechallenge:	positive- 8
Rechallenge:	no patient was rechallenged
Report year:	1991-4, 1992-2, 1993-4, 1996-1, 1998-2
Report type:	15-day-6, periodic-5, direct-2

The mean age of the patients was 77.3 years. The mean onset was 26.6 days after instituting therapy with etodolac. Seven cases reported time to onset. There was a 3.3:1 predominance of females. The dose of etodolac was within the labeled dosing in all cases in which the dose was reported. Based on the 4 cases in which an increase from baseline serum creatinine was reported, the mean increase in serum creatinine was 2.7 mg/dL (range 2-3.9). The data were not sufficient to support a finding of a dose-response effect on serum creatinine. In three of the four cases in which a change in serum

creatinine from baseline was reported, the patient was receiving 600 mg of etodolac a day.

Eleven of the 13 patients who developed renal failure had risk factors for acute renal failure in addition to taking etodolac. These additional risk factors included baseline chronic renal insufficiency, concomitant angiotensin converting enzyme inhibitor, concomitant diuretics, concomitant methotrexate, concomitant NSAIDs, congestive heart failure, hypercalcemia, hypertension, hypotension, and metastatic malignancy. Many patients had more than one additional risk factor. Three patients had chronic renal insufficiency before beginning etodolac.

Three patients died, and in another case the reporter considered the episode life-threatening.
Two of the deaths appear to be directly attributable to renal failure. In the third case resulting in death, renal failure apparently resulted in decreased methotrexate excretion and an increased methotrexate plasma concentration. Pancytopenia related to increased methotrexate plasma concentration resulted in the death of the patient.

Eight patients recovered after the drug was discontinued. In the three cases in which timeframes are provided on recovery to baseline serum creatinine, recovery occurred in three days, three weeks, and two months. In another case a drop in serum creatinine from 3.1 to 2.1 mg/dL occurred within two days of discontinuation of etodolac. However, information on further recovery is not known, and the patient's baseline serum creatinine was not provided. Nonspecific qualitative statements regarding recovery were provided in four cases; for example, the reports described the patients' conditions after discontinuation of the etodolac as "subsequently recovered," "slowly recovered," "subsequent improvement," and "recovered."

Two cases are presented below.

1. AERS 5004660, MFR 893146009S, US (ME), 1993
A 78-year-old woman with a prior medical history of hypertension, arteriosclerotic heart disease, and cerebral vascular accident, but no prior history of renal function impairment, was prescribed etodolac 600 mg a day for osteoarthritis. Concomitant medications included atenolol and chlorthalidone. After an unknown period of time, the dose of etodolac was increased to 900 mg a day because the patient was not receiving sufficient effect with the dose initially prescribed. After a "short" but unspecified period of time, the patient was admitted to the hospital with a 3-to-4-day history of progressive shortness of breath and weakness. Scattered rales were noted in the lower lung fields on examination. A chest x-ray was consistent with congestive heart failure. Blood urea nitrogen was 123 mg/dL, and serum creatinine was 9.8 mg/dL. The patient did not respond to treatment with fluid challenge, intravenous furosemide and dopamine, and she died after 8 days of hospitalization.

2. AERS 48039048, Direct, US (GA), 1991
A 75-year-old woman with a prior medical history of hypertension, hypertrophic cardiomyopathy, tachyarrhythmias, and noninsulin dependent diabetes mellitus was prescribed etodolac for osteoarthritis and back pain. Concomitant medications included digoxin and furosemide. After taking etodolac for 4

days, she presented to the emergency room with severe fatigue and confusion. She was diagnosed with renal failure and digoxin toxicity, and she was admitted to the hospital. Serum creatinine on admission was 5.9 mg/dL, up from her baseline of 2 mg/dL. Etodolac was discontinued, and the patient recovered.

Celecoxib(122)

Descriptive statistics for the renal failure case series are provided in the attached Table 2. Additional demographics include:

Daily dose:	Range 100-800 mg, median 200 mg, mean-224 mg (n=88)
Dechallenge:	Positive- 55
Rechallenge:	Positive-2
Report type:	15-day-20, periodic-59, direct-43

The median age was 72 years (see Table 1). Age and gender was not stated in 18 and 14 reports respectively. Among the cases where gender was reported there was a preponderance of females. Eighty-one (66%) cases mentioned time of onset of renal failure from the start of Celebrex therapy, and the median time was 18 days. In 4(3%) of cases the time of onset of renal failure was less than or equal to 3 days and in 33(27%) cases this was less than or equal to 14 days. Dose was mentioned in 88 (72%) reports and it was within the labeling recommendation in all patients except one. One patient received at least twice the recommended dose of Celebrex [400 mg twice a day (800 mg total daily dose)] for his unspecified backache (off-label indication) and osteoarthrosis. Serum creatinine (SCr) changes (peak SCr minus baseline SCr) were reported in 44 cases (36%). The mean SCr change was 2.9 mg/dl. In all 30 cases where SCr changes were reported 2 or above (range 2-7.6 mg/dl), the reported total daily dose of Celebrex was within the recommended dosage. Positive dechallenge was noted in 55(45%) cases and positive rechallenge in 2 of these cases which are described later. Sixty-four percent of the patients were hospitalized and 12 percent underwent dialysis. In nearly 20 percent of cases the reporter considered that the adverse renal event was life threatening. Eight (6%) patients died and these can be attributed to renal failure in association with Celebrex use.

All cases presented with risk factors for renal failure aside from Celebrex use with the exception of 26 (21%) case reports, which did not state any risk factors. The common risk factors included disease states such as hypertension, diabetes mellitus, congestive heart failure and concomitant medications such as diuretics, ACE inhibitors, and NSAIDs. Forty-five cases reported a baseline SCr. Of the 45 cases many of which might indicate normal baseline function, 15 (33%) had a baseline SCr $\leq$ 1.0 mg/dl, 27 (60%) had a baseline SCr $\leq$ 1.2 mg/dl, and 32 (71%) had a baseline SCr $\leq$ 1.5 mg/dl. In sixteen percent of cases, who had pre-existing renal disease or renal insufficiency or renal impairment (12 cases), and chronic renal insufficiency or renal disease or renal failure (8 cases), worsening of renal condition resulting in renal failure was observed in this case series. There were 2 (1.6%) cases with apparently normal kidney function and no history of renal problem who experienced renal failure. In one of these two cases, the time of onset of renal failure was 4 days and 30 days in the other.

Two representative cases follow:

1. ISR#3410368-0; Direct Report; US (MA); 1999
A 78-year-old female with a history of hypertension, coronary artery disease, diabetes mellitus, and peripheral neuropathy was started on celecoxib 200 mg (unspecified frequency) for osteoarthritis. Her baseline SCr was 1.1 and BUN 16. Approximately 120 days later her SCr increased to 3.1 and BUN to 40 and her medications namely Celebrex, captopril, HCTZ were discontinued. At that time she was also on sulfamethoxazole plus trimethoprim for her UTI and this combo was also discontinued. About 35 days later her SCr was 1.2 and BUN 20. Nearly two months later her SCr was 1.2 and BUN 29 and Celebrex 100mg QD was restarted. About 12 days later her SCr increased to 2.0 and BUN 42 and Celebrex was stopped. A week later her SCr was 1.4 and BUN was 30. Concomitant medications included atenolol, simvastatin, insulin and sertraline.

2. ISR# 3488770-0; Mfr# 991208-SK443; US (ND); 2000
A physician reported that an 88-year-old female under his care on celecoxib therapy for unspecified disease/dose/duration went into acute renal failure (ARF) for which she was hospitalized for 10 days. Per her physician the ARF resolved rapidly after unspecified therapy. Within a month the physician restarted her on celecoxib and she was hospitalized again with ARF and had to undergo dialysis. Her SCr rose to 4.3 and BUN to 58. Celecoxib was discontinued and she again responded to unspecified therapy. There is no mention of concomitant illness or meds.

Rofecoxib (142)
Descriptive statistics for the renal failure case series are provided in the attached Table 3. Additional demographics:

Daily dose:	Range 12.5-50 mg, median 25 mg, mean 26.6 mg
Rechallenge:	Positive - 1
Report type:	15-day-108, periodic-0, direct-34
Report year:	2000-114, 1999-28

The patients were predominantly female and the average age was 73 years (range = 33 - 101 years). Twenty-nine cases (20%) did not report age and 18 cases (13%) did not report gender. Nearly 70% required hospitalization and 15% reported the need for dialysis. Death, due to renal failure, which attributed the cause to Vioxx, occurred in 6%. There were only 2 rechallenge cases where one was positive and the other negative at the time of reporting. Cases noting a baseline and peak serum creatinine showed a mean creatinine change of 4 mg/dl (range = 0.4 - 12.9 mg/dl). Those cases reporting a peak and recovery serum creatinine noted an average decline of 2.9 mg/dl (range = 0.4 - 11.1 mg/dl) to recovery. The onset of adverse renal symptoms was reported in 100 cases and occurred at an average of approximately 33 days after the initiation of Vioxx; however, the median was 10 days and 32 cases occurred within 3 days. In all cases the dose of Vioxx fell within the recommended range of 12.5 to 50 mg once daily with a mean of 26.6 mg and a median of 25 mg per day.

Cases where patients were stable on multiple medications were included in the case series. Of the 142 cases, 12 reported normal kidney function or no history of renal dysfunction prior to initiating Vioxx. Fifty-four cases reported a baseline SCr. Of the 54 cases many of which might indicate normal baseline kidney function, 10 (19%) had a baseline SCr ≤ 1.0 mg/dl, 16 (30%) had a baseline SCr ≤ 1.2 mg/dl, and 30 (56%) had a baseline SCr ≤ 1.5 mg/dl. Pre-existing renal disease (chronic renal insufficiency, renal insufficiency, chronic renal failure, history of renal failure) was reported in 20% of the cases.

Common risk factors consist of concomitant disease states and medications and were multiple for most patients. The most prevalent medical condition reported was hypertension (26%), followed by diabetes mellitus (21%), pre-existing or history of renal failure or renal insufficiency (20%), congestive heart failure (17%), hyperuricemia - evidenced by gout or allopurinol use - (9%), and concomitant hospitalization (8%). The most common medications reported were diuretics (43%), followed by selective and nonselective nonsteroidal anti-inflammatories (33%), angiotensin converting enzyme inhibitors (28%), and angiotensin-II receptor antagonists (5%).

Four representative cases follow:

1. ISR# 3498492-8; Direct Report; US (IN); 2000
A 79 year-old female with a history of DM, lymph and peripheral edema, ASHD, and a mastectomy was placed on Vioxx for osteoarthritis. Concomitant medications include Lasix, Zaroxolyn, potassium, and Zestril. The patient was admitted to the hospital 3 and 1/2 weeks later for edema. Laboratory tests showed a SCr = 4.3, BUN = 97, K^+ = 6.8, and Phosphorus = 7.2. The nephrologist diagnosed acute renal failure due to Lasix, Zestril, Vioxx, and potassium. Vioxx was discontinued and the patient was stabilized and discharged. The patient began Vioxx again without the physician's consent and, again, experienced acute renal failure 2 weeks later (SCr = 8.3, BUN = 65, K^+ = 5.5, Phosporus = 10.6).

2. ISR# 3351628-1; Mfr# WAES 99080373; US (MA); 1999
A 73 year-old female with multiple medical problems including osteoporosis, HTN, DM, COPD, a. fib., asthma, and angina developed renal failure, CHF, digoxin toxicity, and thrombocytopenia after 1 week of Vioxx. Admission labs revealed SCr = 2.2, BUN = 50, pH = 7.1, K^+ = 7.0, and digoxin = 5.6 (baseline labs: SCr = 1.7, BUN = 25-28, and digoxin < 2.0). She experienced a cardiac arrest, was intubated, and revived. She also required hemodialysis.

3. ISR# 3460052-2; Direct Report; US (IL); 2000
A 78 year-old male with a SCr = 1.4 and digoxin = 1.9 five days prior to initiating Vioxx developed an elevated SCr of 3.7 and a digoxin level of 4.2 four days after beginning Vioxx. Vioxx was discontinued and Digibind was administered. His SCr was 2.5 six days after discontinuation.

4. ISR# 3490859-7; Direct Report; US (IA); 2000
An 84 year-old female with multiple medical problems including DJD, osteoporosis, and renal vascular

disease was prescribed Vioxx 12.5mg daily. After 3 weeks, the dose was increased to 25mg daily and after 1 week, her SCr had increased from a baseline of 1.6 to 3.7 and her BUN increased from 33 to 81. Concomitant medications were glucosamine, meclizine, and levothyroxine.

SUMMARY

Etodolac

We evaluated 13 cases of renal failure in the AERS database temporally related to therapy with etodolac. Most of the cases occurred in high-risk elderly patients. Eighty-five percent of the patients in the case series had risk factors for renal failure in addition to taking etodolac. Many patients had more than one additional risk factor for renal failure. Two patients in the series died due to renal failure.

The prevalence of risk factors in the patients in the case series suggests that patients at increased risk for renal function impairment should be monitored closely while taking etodolac.

Celecoxib

Serious renal toxicity including acute renal failure leading to fatalities has been reported in association with Celebrex use. One hundred and twenty-two domestic cases of Celebrex-associated renal failure have been identified in the FDA's AERS database. The current labeling of Celebrex mentions acute renal failure, interstitial nephritis, increased BUN and creatinine under the *Adverse Reactions* section. Under the *Precautions* section, the *Renal effects* statements regarding renal decompensation indicate that patients at greatest risk of this reaction are those with impaired renal function and other diseases. While it is true that patients at greatest risk of renal failure are those with risk factors, there were cases with apparently normal kidney function that have also been reported with renal failure while on Celebrex. Additionally, the *Precautions* section implies renal injuries occur from long-term administration of NSAIDs. Our review shows that 27% of the cases occurred within two weeks and 3% within 3 days. Finally, the labeling has no reference to renal toxicity in the Information for Patients section.

Rofexocib

One hundred and forty-two cases of renal failure temporally associated with Vioxx were evaluated. The patients were mostly elderly females with multiple risk factors. Cases reporting risk factors commonly included pre-existing disease states: hypertension, diabetes mellitus, renal dysfunction, congestive heart failure, hyperuricemia, and medications: concomitant diuretics and/or angiotensin converting enzyme inhibitors, and conversion from a nonselective NSAID to a selective COX-2 inhibitor.

It is interesting to note that of the 100 cases that reported a time to onset of renal symptoms, 32 cases occurred within 3 days. The majority of patients recovered upon discontinuation of the medication; nevertheless, greater than 15% reported the need for dialysis, nearly 70% required hospitalization, and

greater than 6% attributed death due Vioxx-initiated renal failure. The dose did not appear to be a factor as all dosing was within the recommended range. Pre-existing renal disease (chronic renal insufficiency, renal insufficiency, chronic renal failure, history of renal failure) was reported in 20% of the cases. Twelve reported normal kidney function or no history of renal dysfunction prior to initiating Vioxx.

Our findings are consistent with the current labeling under *Precautions* in that patients at greatest risk are those with impaired renal function, heart failure, those taking diuretics, ACE inhibitors, and the elderly. However, the labeling refers to the risks of long-term administration and it was noted in the evaluation of our case series that nearly one-third of our cases reported an acute onset (0-3days). Finally, both *Clinical Pharmacology* and *Warnings* mention that no safety information is available regarding the use of Vioxx in patients with advanced kidney disease**.**

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cc:
HFD-430/Beitz/Trontell/Chen/Weaver/Ahmad/Kortepeter/Brinker
1/7/2001/COX2Renaldocument2

Table 1. Descriptive statistics for the etodolac renal failure case series (n=13)

Attribute		
Age (years)	Median	77
	Mean	75.8
	Range	72-84
Sex	%Female	76.9
	%Male	23.1
Onset (days)	Median	28
	Mean	26.6
	Range	4-45
Cases with onset @ <=3 days		0
Creatinine change	Median	2.4
	Mean	2.7
	Range	2-3.9
Outcome (% appearance)		Hospitalized (69.2) Life threatening (7.7) Death (23.1)
Dose	Median	600
	Mean	611
	Range	400-900
Cases over rec. dose**		0

** >1,000 mg per day

Table 2. Descriptive statistics for the celecoxib renal failure case series (n=122)

Attribute		
Age (years)	Median	72
	Mean	69.7
	Range	14-101
Sex	%Female	62.0
	%Male	38.0
Onset (days)	Median	18
	Mean	41.7
	Range	1-300
Cases with onset @ <=3 days		4
Creatinine change	Median	2.4
	Mean	2.9
	Range	0.5-7.6
Outcome (% appearance)		Hospitalized (67.2) Life threatening (19.7) Dialysis (12.3) Death (6.6)
Dose	Median	200
	Mean	224
	Range	100-800
Cases over rec. dose**		1

** >400 mg per day

Table 3. Descriptive statistics for the Vioxx renal failure case series (n=142)

Attribute		
Age (years)	Median	75
	Mean	73.1
	Range	33-101
Sex	%Female	68.5
	%Male	31.5
Onset (days)	Median	10
	Mean	32.7
	Range	1-450
Cases with onset @ <=3 days		32
Creatinine change	Median	3.3
	Mean	4.0
	Range	0.4-12.9
Outcome (% appearance)		Hospitalized (69.9) Life threatening (23.1) Dialysis (15.4) Death (6.3)
Dose	Median	25
	Mean	26.6
	Range	12.5-50
Cases over rec. dose**		0

** > 50 mg per day

Appendix 1

Criteria for excluding cases for further review or analysis

- Events not related to the drug administration, e.g., renal failure reported while patient had car accident and went into multi-organ failure
- Events resulting from the previously existing underlying renal disorder
- Events more related to (or confounded by) another suspect drug (2 suspects reported) or concomitant drug(s), based on their therapy dates, and the other drug(s) is labeled for renal failure
- Events for which causality cannot be assessed due to multiple suspect drugs (3 or more)
- No evidence that the patient received the drug, including unconfirmed second hand report
- No evidence that the event of interest occurred including unconfirmed second hand report (i.e., reporter was notified by competitor's drug representative)
- Evidence of hepatorenal syndrome (concomitant liver and renal failure)
- Renal failure precipitated by concomitant rhabdomyolysis, acute GI bleed, sepsis
- Fluid retention with no indication of renal failure
- Event did not meet the case definition for renal failure described above

Appendix 2

Criteria for Probable cases

- No past history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration the patient developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. No concomitant drugs reported.
- Patient with a past history of renal insufficiency, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. No concomitant drugs reported.
- Patients with or without a past history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition. Events abated only after suspect drug discontinuation. Concomitant drugs which were not labeled for renal failure were continued.

Criteria for Possible cases

- Baseline serum creatinine/BUN were elevated possibly indicating a chronic renal disorder but the patient developed diagnosed renal failure/acute renal failure only after suspect drug administration supported by changes in of serum creatinine/BUN meeting the case definition. The patient is at risk for developing renal failure due to the abnormal baseline.
- No history of renal insufficiency or disorder, normal baseline serum creatinine/BUN, within a reasonable time after drug administration developed diagnosed renal failure/acute renal failure supported by changes in serum creatinine/BUN meeting the case definition, events abated after drug discontinuation. There were standing concomitant drugs which may or may not be labeled for renal failure.
- The patient is reported to have diagnosed renal failure but with insufficient lab data to support the diagnosis from a health care provider or consumer and can not exclude the possibility that the drug is associated with the events (e.g., because of drug therapy date).
- The patient is reported to require dialysis or kidney transplant while on drug with insufficient lab data and can not exclude the possibility that the drug is associated with the event, based on the drug therapy date.